

Implementing Metrological Traceability in Laboratory Medicine: JCTLM Role

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Outline

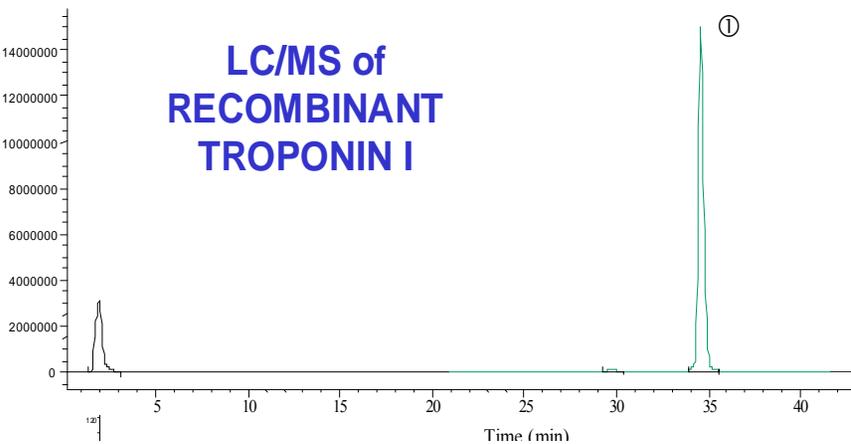
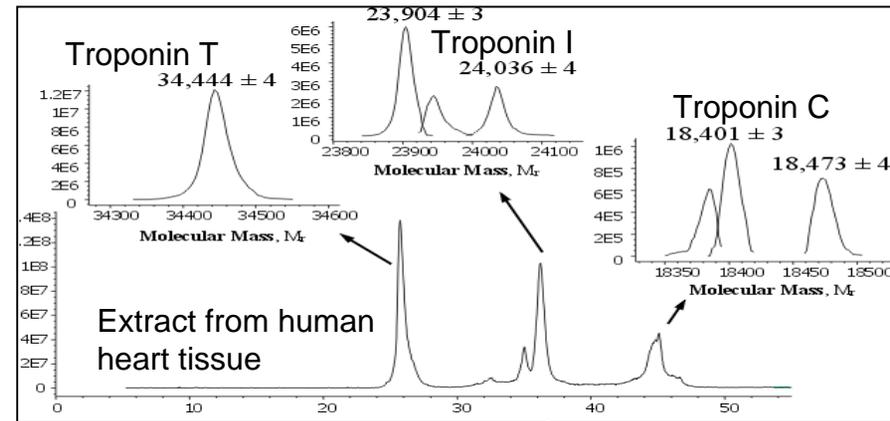
- Drivers for Improved Quality in Clinical Measurements
- EU IVD Directive ↔ JCTLM
- Activities of the JCTLM

Drivers for Improved Quality in Clinical Measurements

- U.S. HC Measurement Costs
 - U.S. Spends ~ \$1.5 trillion on Health Care
 - ~10-15% associated with measurement
 - Non-diagnostic measurements cost ~\$40B
- German Health report 1998
 - Costs of repeat measurements amounts to **1.5 B US\$** per year in Germany
- Medical Decision-Making
 - Incorrect diagnosis and treatment
 - Impairment of patient well-being
- Competitiveness and International Trade
 - FDA Medical Devices Legislation
 - EU IVDD

Assay	Conc.	# Labs
Manufacturer	ng/mL	
A	19.9	115
B	6.7	489
C	0.85	27

From G. S. Bodor, Denver Health and Hospitals -- personal communication 1997



PROBLEM:

Troponin I is a complex, heterogeneous protein that may be free or may be complexed with Troponin C and/or Troponin T. Different assay antibodies do not recognize the same form.

NIST Response:

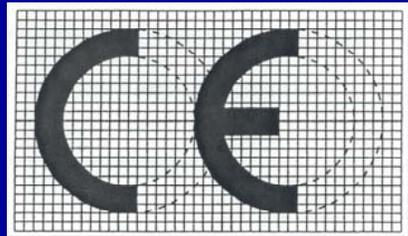
- Completed two round-robins involving 20 assay kits from 12 different manufacturers worldwide to identify best material for calibrating Troponin-I assays. Use of this material reduced variation by factor of 10.
- Material selected for use as SRM 2921 is a Troponin - I, C, T - complex from human heart tissue. Concentration will be certified at NIST.
- Future plans are to develop a reference method and SRM for Troponin I in blood.

New International Regulatory Driver: EU IVD Directive



Implementation begins in December, 2003

- Worldwide *in vitro* diagnostic device market is ~\$20B
- **> 60% of European market is supplied by U.S.**



Stated Purpose of Directive

- Eliminate trade barriers *within Europe* by ensuring access to the entire EU market with one single product approval (CE Mark)

Essential Requirements

- IVD Calibrators and/or control materials must be traceable to **“standards of a higher order”**
- nationally/internationally recognized *certified reference materials*

Scheduled Implementation

- First IVD product with CE Mark may be placed from June 2000 onwards
- All *new* IVD products *must* have mark by December 2003
- Existing IVD products may be sold without the CE mark until December 2005



European Commission

Enterprise Directorate-General

“... the traceability of values assigned to calibrators and control materials must be assured through available reference measurement procedures and/or reference materials of a higher order ...”

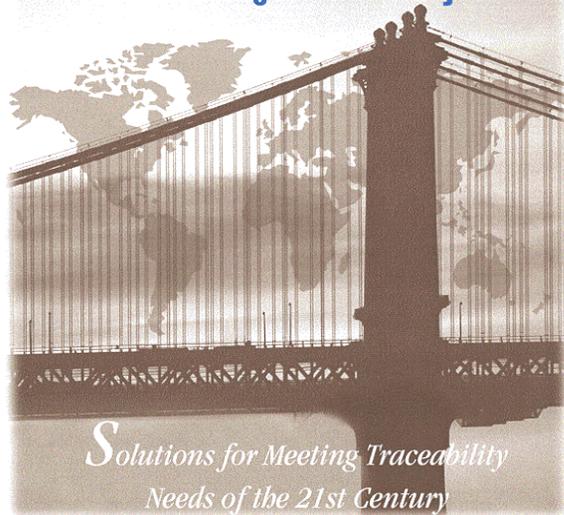
Annex 1 (3) 2nd para

IVD Manufacturers have requested that NMIs develop internationally recognized reference methods and CRMs to meet this assist them in meeting this traceability requirement.

W o r k s h o p O n

Measurement Traceability

For Clinical Laboratory Testing
and In Vitro Diagnostic Test Systems



November 2-3, 2000 • Gaithersburg, MD

NIST

National Institute of Standards and Technology
Technology Administration, U.S. Department of Commerce

Attendees included:

- IVD Manufacturers
- Regulatory Agencies and Notified Bodies
- Providers of Proficiency Testing Programs,
- Laboratory Accreditation, and Measurement Quality assessment Materials
- Laboratory professionals involved in standardization of laboratory methods
- International Standards Laboratories

JOINT COMMITTEE on TRACEABILITY in LABORATORY MEDICINE



JCTLM
a global initiative,
formed
in Paris, June 12, 2002

JCTLM is Composed of Three Principals and Two Working Groups

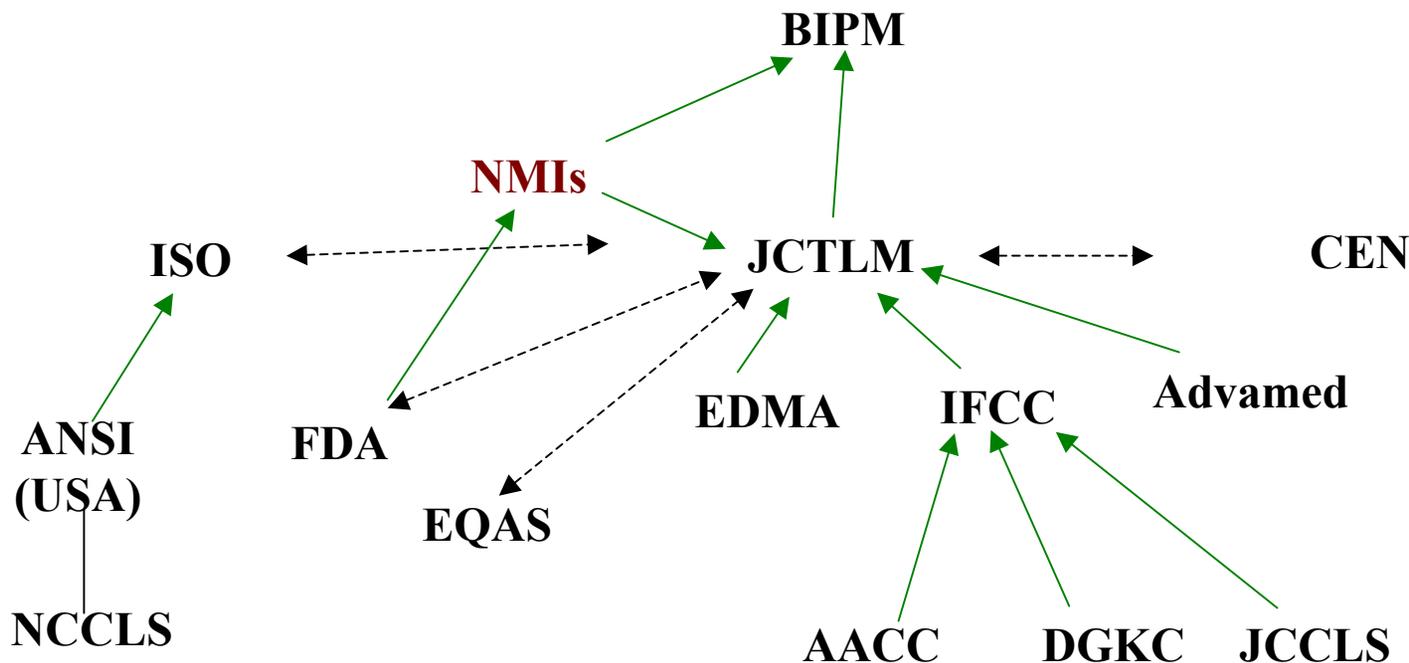


Principals

- NMIs via CIPM/BIPM
- IFCC
- ILAC

Working Groups

- Reference Materials and Reference Procedures
 - *Implementation Protocols*
- Reference Laboratory Networks



JCTLM Working Group on Reference Materials and Reference Measurement Procedures

Charge:

- **establishing a process for identifying, and reviewing against agreed upon criteria** “higher order” Certified Reference Materials and Reference Measurement Procedures required for IVD industry compliance with the EC IVD Directive regarding in vitro diagnostic medical devices.
- **publishing a List** of “higher order” Certified Reference Materials and Reference Measurement Procedures required for IVD industry compliance with the EC IVD Directive regarding in vitro diagnostic medical devices.
- *Co-Chairs: Willie E. May (NIST)
Heinz Schimmel (EU IRMM)*

JCTLM Working Group on Reference Laboratory Networks

Charge:

- Collecting information on existing and candidate reference measurement laboratories (RMLs)
- Encouraging and facilitating the formation of networks of RMLs for different groups of measurable quantities (concerning electrolytes, substrates/metabolites, enzymes, HbA1c, low molecular hormones, etc.)
- Establishing a procedure for the approval of RMLs on the basis of their metrological level according to ISO 15195 and their performance as demonstrated in inter-laboratory comparisons linked to an NMI.

Co-Chairs: Professor Dr. Lothar Siekmann, University of Bonn (Germany)
Professor Dr. Linda Thienpont, University of Gent (Belgium)

CEN and ISO work related to metrological traceability of IVD MDs

Presentation of **reference measurement procedures** (EN 12286:1998 + 12286/A1:2000; ISO/FDIS 15193)

Description of **reference materials** (EN 12287:1999, ISO/FDIS 15194)

Metrological **traceability** of values assigned to calibrators and control materials (prEN ISO/FDIS 17511)

Metrological **traceability** of values for catalytic concentration of **enzymes** assigned to calibrators and control materials (prEN ISO/FDIS 18153)

Laboratory medicine - Requirements for **reference measurement laboratories** (prEN ISO/FDIS 15195)

Joint Committee on Traceability in Laboratory Medicine

JCTLM

Review Teams for Highest Priority Analyte Areas

Worldwide representation from Lab Accreditation Organizations, NMLs, Professional Societies , and IVD Industry

Electrolytes

Enzymes

Metabolites and Substrates

Proteins

Nucleic Acids

Drugs

Hormones

Coagulation Factors

JCTLM Highest Priority Analyte Categories & Review Team Leaders

Analyte Category

Review Team Leaders

(With representative examples)

Coagulation Factors

Elaine Gray, NIBSC

WHO 2nd International Standard for Antithrombin Plasma, Human

WHO 1st International Standard for Beta Thromboglobulin Human purified

Drugs [therapeutic and “of abuse”] **Andre Henrion, PTB**

Digoxin/ Digitoxin

Theophylline

Cocaine

THC-COOH

Electrolytes

Richard Miller, Dade Behring

Calcium

Potassium

Sodium

Enzymes

Mauro Panteghini, Azienda Ospedaliera “Spedali Civili”

AMYLASE

CK

GGT

JCTLM Highest Priority Analyte Categories & Review Team Chairs – cont'd

Analyte Category

(With representative examples)

Review Team Chair

Metabolites and Substrates

Cholesterol

Creatinine

Glucose

Michael Welch, NIST

Nucleic Acids

Hepatitis A virus RNA,

Hepatitis B virus DNA

Helen Parkes, LGC

Non-Peptide Hormones

Cortisol

Estradiol-17 β

Thyroxine

Heinz Schimmel, IRMM

Proteins

Albumin

Troponin-I

PSA

David Sogin, Abbott Laboratories

The Electrolytes Review Team:

- Dr. W. Külpmann, MH-Hannover (Germany)
- Dr. S. Long, NIST (USA)
- Dr. P. D'Orazio, IL (USA)
- Dr H. Schimmel, IRMM (Belgium)
- Dr. L. Penberthy, Flinders Med. Ctr. (Australia)
- C. Jain, Beckman (USA)
- Dr. K. Kuwa, Univ. Tskuba (Japan)
- Dr. L. Ma, NRCCRM, (China)
- R. Miller Dade Behring (USA)

Nominated Reference Methods and Reference Materials (Cycle I)

	Reference Methods 79	Reference Materials 436
Blood Gases		2
Coagulation Factor		28
Drugs	3	84
Electrolytes	20	64
Enzymes	6	8
Hormones	21	10
Metab. & Substrates	22	62
Non-Electrolyte Metals	3	62
Nucleic Acids		4
pH		1
Proteins	3	51
Vitamins		9
Other		58

JCTLM WG-I Classification Scheme

- **Review Teams sorted all nominated Reference Materials and Reference Measurement Procedures based on their assessment of compliance with relevant ISO Standards**
 - α list **Fully Compliant**
 - β list **Provisionally Acceptable**
 - γ list **Does Not Meet Requirements**
- **α and β category nominations to be merged into a single list and submitted for JCTLM Executive consideration (without distinction). List to contain two categories {see next slide}**
- **Each Review Team will keep track of the nominations by category and solicit missing and/or clarify information regarding all β category nominations for discussions at next Working Group-I Meeting to determine if these nominations should remain on the List for 2005**

Initial Provisional Lists of Higher Order Reference Materials and Reference Measurement Procedures

- I. Certified Reference Materials and Reference Measurement Procedures for well-defined chemical entities or internationally recognized reference method-defined measurands, such as enzymes. Reference Materials included in this category are those that are traceable to the SI units. [***Electrolytes, Enzymes, Drugs, Metabolites and Substrates, Non-Peptide Hormones, some Proteins***]

- II. International Conventional Reference Materials, i.e., where the measurand(s) is/are not metrologically traceable to the SI but, which by international agreement, are used as reference values for a defined quantity [e.g., *WHO reference materials for **Coagulation Factors, Nucleic Acids, some Proteins***]

Reference Measurement Procedures

Analyte Name	Procedure Name and/or ID #	Applicable Matrices	Measurement Principle
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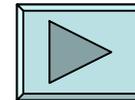
Reference Procedure Citation(s) or Document(s)	Reference Procedure Comparability Assessment Studies
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Higher Order Reference Measurement Procedures for Cholesterol in Serum

Reference Measurement Procedures					
Analyte Name	Procedure Name and/or ID #	Applicable Matrices	Measurement Principle	Reference Procedure Citation(s) or Document(s)	Reference Procedure Comparability Assessment Studies
cholesterol	DGKC definitive Method for Serum Cholesterol	lyophilized, fresh, or frozen human serum or plasma	ID/GC/MS	Siekmann et al., Z. anal. Chem. 279, 145-146 (1976)	PTB - National Key Comparison for Accreditation
cholesterol	CDCAbell-Kendall method for cholesterol	lyophilized, fresh or frozen human serum	Spectrophotometry	Cooper, GR, et al, Clin Chem 32: 921-929, 1986	Clin Chem 36, 370-375 (1990)
cholesterol	NIST definitive method for serum cholesterol	lyophilized, fresh, or frozen serum	ID/GC/MS	Anal Chem 61, 1718-1723 (1989)	CCQM-K6; http://kcdb.bipm.org/appendixB/appbresults/ccqm-k6/ccqm-k6_final_report.pdf ; Clin Chem 36, 370-375 (1990)
cholesterol	U. Of Ghent reference method for cholesterol	lyophilized, fresh, or frozen serum	ID/GC/MS	Clin Chem 39,1001-6 (1993) [=part II of Clin Chem 39,993-1000 (1993)]; Eur J Clin Chem Clin Biochem 34, 853-60 (1996); Clin Chem 42, 531-5 (1996)	EUROMET 563

Higher Order Reference Measurement Procedures: Other Analytes

Searchable Provisional List:



Reference Materials

Information about Material

Contact Information

Analyte	Matrix	Material Name and/or ID #	Estimated * Availability (months, as of Jan 2004)	- Producer - Country - Website - Email Address - Phone Number - Fax Number

References

Commutability Study Information and/or Citations	Other Relevant Publications	Hyperlink to Comparability Assessment Studies	Comments

Higher Order Reference Materials: Neat Cholesterol

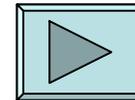
Reference Materials							
Information about Material			Contact Information	References	References		
Analyte	Matrix	Material Name and/or ID #	<ul style="list-style-type: none"> - Producer - Country - Website - Email Address - Phone Number - Fax Number 	Commutability Study Information and/or Citations	Other Relevant Publications	Hyperlink to Comparability Assessment Studies	Comments
cholesterol	neat cholesterol crystalline material	GBW09203b	NRCCRM China Tel: 086-10-64221811 Fax: 086-10-64213149 Email: crmservice@nrccrm.com.cn	Primary calibrator for higher order reference methods			
cholesterol	neat cholesterol crystalline material	SRM 911b	NIST USA http://ts.nist.gov/ts/htdocs/230/232/232.htm Email: srminfo@nist.gov	Primary calibrator for higher order reference methods			

Higher Order Reference Materials: Cholesterol in Serum

Reference Materials			Contact Information	References	References		
Analyte	Matrix	Material Name and/or ID #	- Producer - Country - Website - Email Address - Phone Number - Fax Number	Commutability Study Information and/or Citations	Other Relevant Publications	Hyperlink to Comparability Assessment Studies	Comments
cholesterol	human serum	JCCRM 211	HECTEF Japan http://www.in8.co.jp/hectef/start_e.htm Tel: 81-44-813-0055 Fax: 81-44-813-0224			NIST study presented at JCTLM Meeting, June 20, 2003, BIPM, Sevres, France	
cholesterol	human serum (frozen)	SRM 1951b	NIST USA http://ts.nist.gov/ts/htdocs/230/232/232.htm Email: srminfo@nist.gov Tel: (301)975-6776 Fax: (301)948-3730	Material prepared following NCCLS Document C37-A "Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures; Approved Guideline" Method used for certification:		Previous lot (1951a) was measured in NIST study presented at JCTLM Meeting, June 20, 2003, BIPM, Sevres, France	
cholesterol	human serum (lyophilized)	SRM 1952a	NIST USA http://ts.nist.gov/ts/htdocs/230/232/232.htm Email: srminfo@nist.gov Tel: (301)975-6776 Fax: (301)948-3730		Method used for certification: Anal Chem 61, 1718-1723 (1989)	NIST study presented at JCTLM Meeting, June 20, 2003, BIPM, Sevres, France	
cholesterol	human serum (lyophilized)	SRM 968c	NIST USA http://ts.nist.gov/ts/htdocs/230/232/232.htm Email: srminfo@nist.gov Tel: (301)975-6776 Fax: (301)948-3730		Method used for certification: Anal Chem 61, 1718-1723 (1989)	NIST study presented at JCTLM Meeting, June 20, 2003, BIPM, Sevres, France	
cholesterol	human serum (lyophilized)	SRM 909b	NIST USA http://ts.nist.gov/ts/htdocs/230/232/232.htm Email: srminfo@nist.gov Tel: (301)975-6776 Fax: (301)948-3730		Certification process described: Fresenius' J. Anal. Chem. 361:2 71-80 (1998); Method used for certification: Anal Chem 61, 1718-1723	NIST study presented at JCTLM Meeting, June 20, 2003, BIPM, Sevres, France	

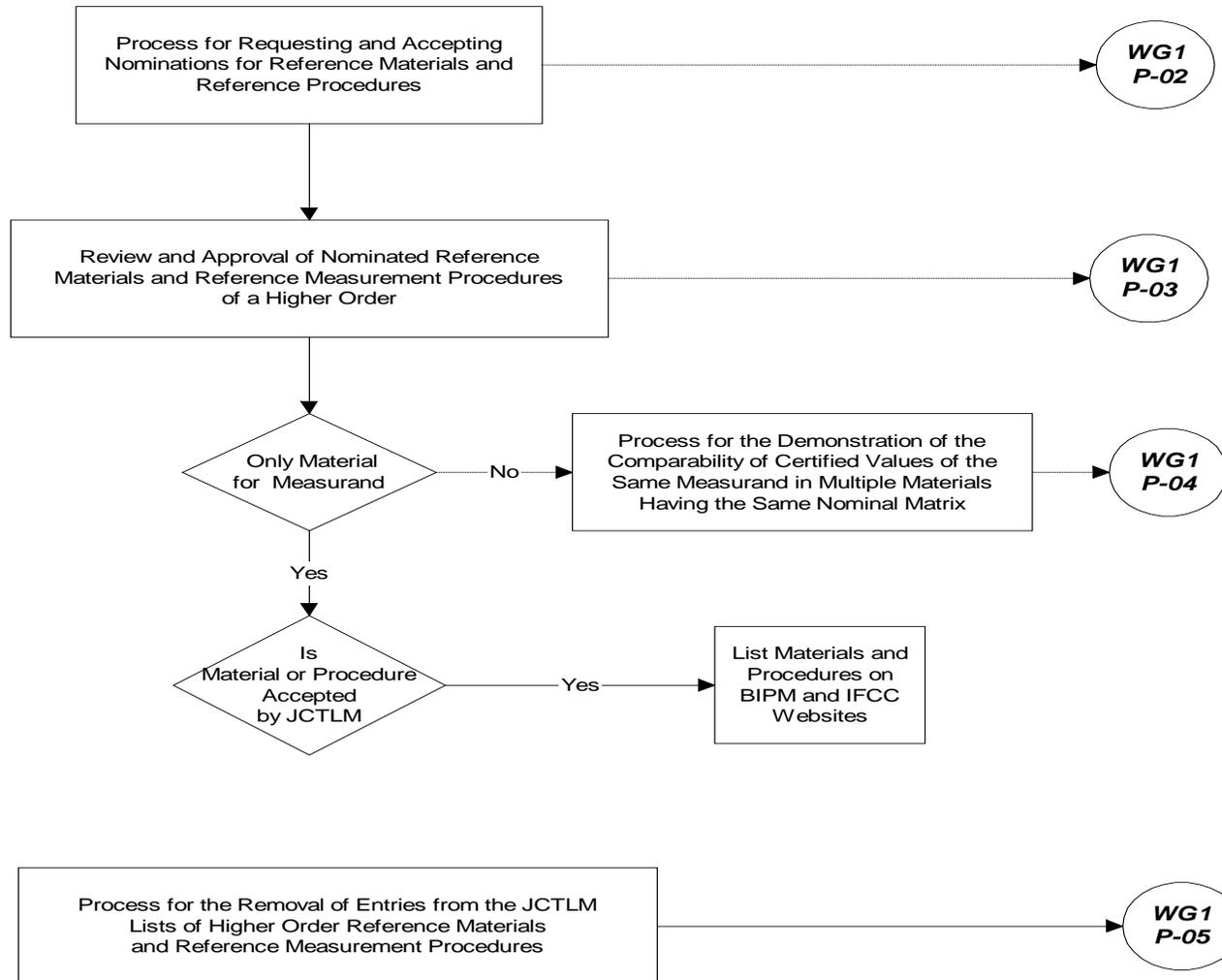
Higher Order Reference Materials: Other Analytes

Searchable Provisional List:



Outline - WG1-P-01

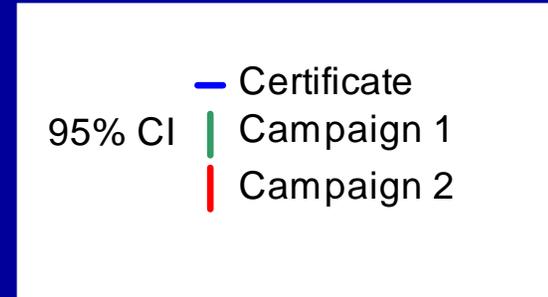
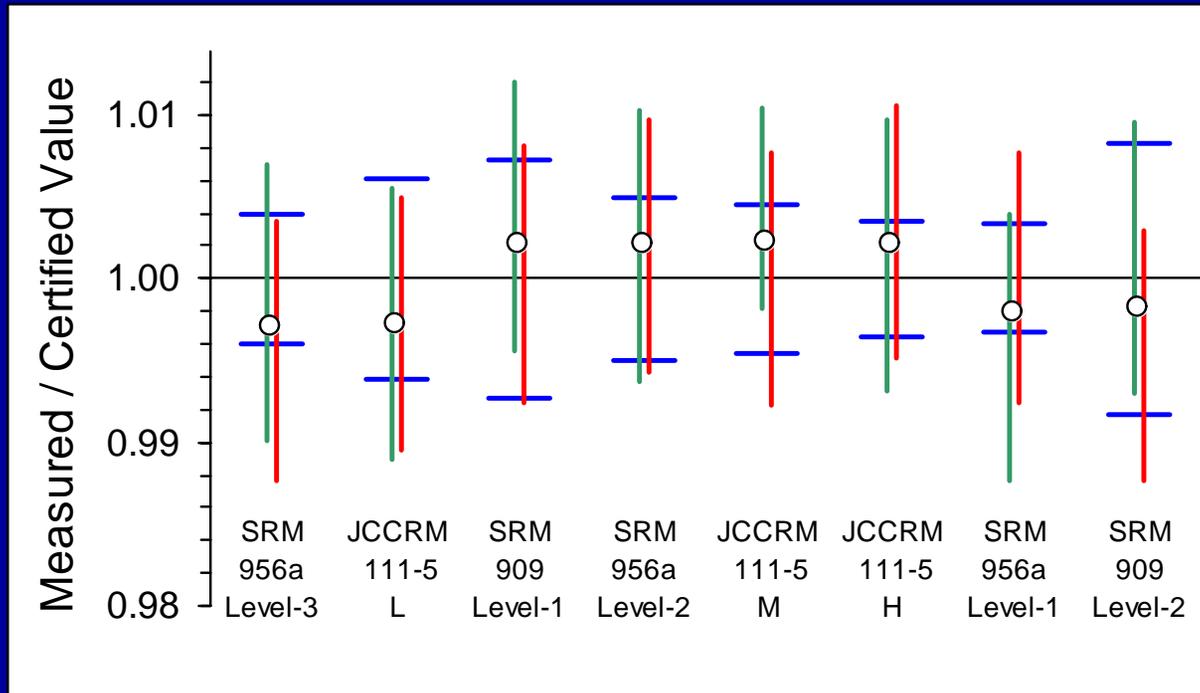
Procedure Code



JCTLM WG-I

- **All Listed Reference Materials and Reference Methods to be Tested to assess comparability**
 - to assess veracity of the Normative Standards-Based Review Process
- **Each Review Team to perform Gap Analysis and present list of Highest Priority Needs**

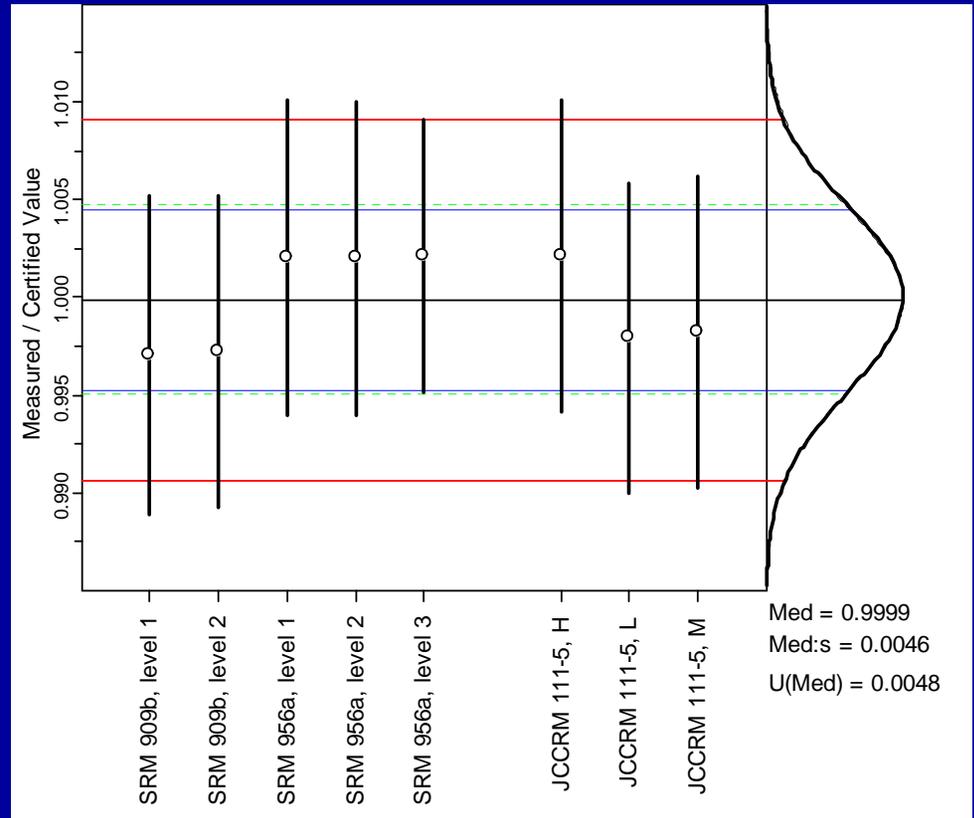
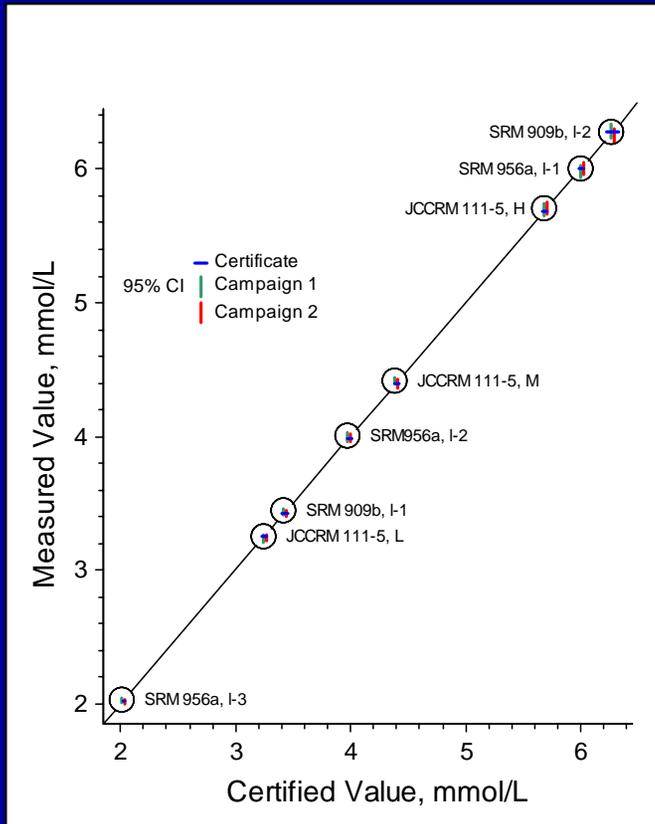
Comparability Assessment for Potassium in Human Serum CRMs on JCTLM List I: Ratio Display



Listed CRMs are all comparable

Potassium in Human Serum CRMs on provisional JCTLM List 1 were assessed for comparability by a single laboratory using a reference measurement procedure under repeatability conditions. The horizontal axis reports the CRMs evaluated. The vertical axis reports the ratio between the measured and certified values of each CRM, X_i/C_i .

JCTLM a-List : Potassium in Serum CRMs



**CRM comparability
independent of analyte
level**

The measured/certified Ratios for this set of CRMs are:

- normally distributed
- centered on the certified values
- with a standard deviation of <0.5%

WG-I Action Items

[based on discussions during JCTLM Executive Meeting]

- **Publish List of Category I Reference Materials and Reference Laboratory Procedures, with descriptive Preamble, by April, 2004** [*Electrolytes, Enzymes, Drugs, Metabolites and Substrates, Non-Peptide Hormones, some Proteins*]
- **Draft separate Preamble and publish List of Category II Reference Materials during the last quarter of 2004 after further discussions among the Working Group** [*e.g. WHO materials for Coagulation Factors, Nucleic Acids, some Proteins*]
- **Proceed with open call for new nominations in original 8 plus the 5 new categories by April 1, 2004**
- **Complete WG-I Quality Manual and present to JCTLM Executive for Adoption by August 1, 2004**

New Areas of Priority and Review Team Leaders

- **Blood Grouping/ Typing** – Susan Thorpe, NIBSC
- **Blood Gases** – Susan Blonshine, NCCLS
- **Microbial Serology** – Morag Ferguson, NIBSC
- **Non-Electrolyte Metals** – L. Yu, NIST
- **Vitamins** – Katherine Sharpless, NIST

Global Action Plan for Addressing IVD Directive: NIST Proposal

- NIST would develop and maintain reference methods and SRMs for up to 40% of the “**Category I**” analytes
- NMIs in the EU, Japan and Australia would develop reference methods and CRMs for the remaining 60%
- Mechanisms for mutual recognition of reference methods and assigned values for CRMs to be established:
 - **Collaboration between NMIs**
 - **Independent Development with Verification**

Classes of Analytes:

“**Category I**” - approximately 100 well-defined chemical species, potentially traceable to SI units

“**Category II**” – less well defined, potentially not traceable to SI units, and number >500 (for example: method dependent analytes such as liver enzymes)

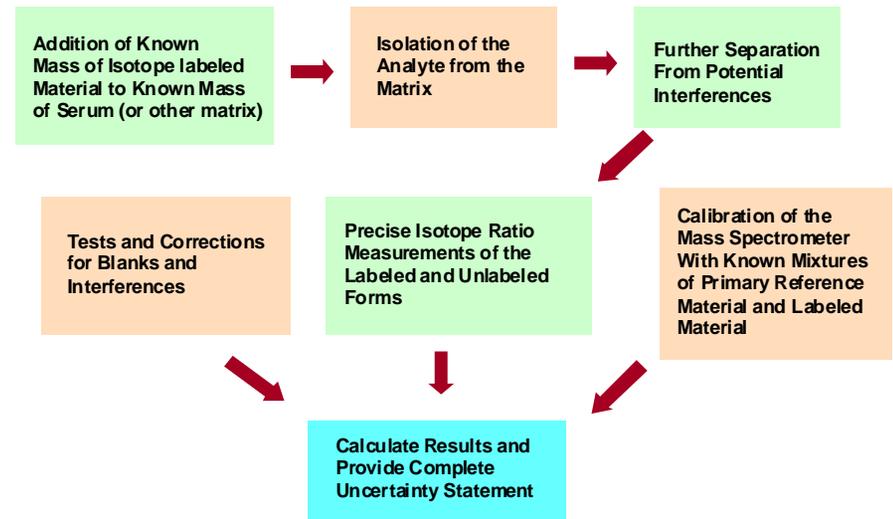
Reference Methods & SRMs for Health Status Markers in Blood/Urine

Reference Systems are Currently in Place for Many Well-Defined Markers that are:

- Relatively small well-defined molecular or elemental species
- Typically, can be determined using ID/MS methodology
- Such as the following:

<u>Marker</u>	<u>Disease State</u>
Calcium	Cancer, Blood Clotting
Chloride	Kidney Function
Cholesterol	Heart Disease
Creatinine	Kidney Function
Glucose	Diabetes
Lithium	Antipsychotic Treatment
Magnesium	Heart Disease
Potassium	Electrolyte Balance
Sodium	Electrolyte Balance
Triglycerides	Heart Disease
Urea	Kidney Function
Uric Acid	Gout
Vitamins	Nutrition Status

Isotope Dilution/Mass Spectrometry-based Definitive Methods

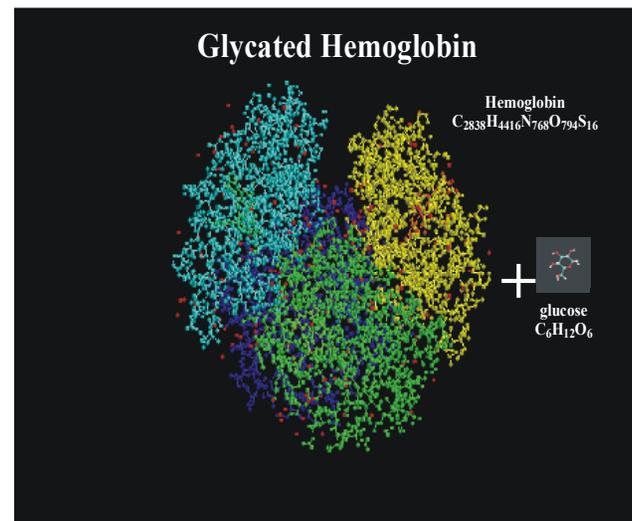


Reference Methods & SRMs for Health Status Markers in Blood/Urine

Reference Systems Being Developed for New Markers that typically exhibit:

- High molecular mass (>20,000 daltons)
- Heterogeneity of analyte
- Low concentration
- Instability of analyte form
- Cannot all be determined using ID/MS or other definitive methodologies
- Such as the following:

<u>Marker</u>	<u>Disease State</u>
Troponin-I	Myocardial Infarction
C-Reactive Protein	Risk of Heart Attack
Homocysteine	Risk of Heart Disease
Glycated Hemoglobin	Diabetes Status
T3, T4 and TSH	Thyroid Function
Speciated Iron	Hemochromatosis
PSA	Prostate Cancer
Cadmium & Mercury	Toxic Metal Poisoning
Folates	Neural Tube Defects



Drivers for NIST Activities:

- Standardization necessary before full medical diagnostic benefit can be realized
- EU IVD Directive
- Well-articulated US “Other-Agency” Needs (FDA, NCI, CDC etc)



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**For further
information:**

NIST <http://www.nist.gov>

CSTL <http://www.cstl.nist.gov>

ACD <http://www.cstl.nist.gov/nist839>